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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/237,291	01/25/1999	JUDY CAROL YOUNG	SYS-2068	9391

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EXAMINER	
SCHMIDT, MARY M	
ART UNIT	**PAPER NUMBER**
1635	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/237,291	Applicant(s) YOUNG ET AL.	
	Examiner Mary M. Schmidt	Art Unit 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 March 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *01 March 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *18-20, 23-27, 31-35, 37-44 and 46-47*.

Claim(s) withdrawn from consideration: _____.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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Continuation of 5. does NOT place the application in condition for allowance because: Applicant argues that the 35 U.S.C. 103 (a) rejection was made after Examiner engaged in "impermissible, hindsight reconstruction to pick and choose among the prior art in order to try to fashion a rejection of the claimed invention." Applicant argues that the Examiner did not show why the Aplicants would have been motivated to combine the references as combined in the last Office Action. Applicants argue that the Examiner has "simply made unsupported statements regarding the asserted motivation of a person of ordinary skill in the art to undertake the components of the claimed invention." Applicant argues that the previous rejection was directed to individual components of the claimed invention but did not provide the motivation that the invention as a whole was obvious. Applicants then note that the Examiner previously wrote in a prior Office Action that "There is a high level of unpredictability in the transgenic stem cell art for expression of transgenes in cultured stem cells." Applicant then argues that "Examiner has not shown how the cited references teach the concentration ranges recited in the claims. The Examiner has cited references where certain factors in the claims were used at certain concentrations, but she has made no showing of how the references teach the recited ranges of concentrations." Finally, Applicant argues that "claims 35, 44 and 51 are directed to CD34+ thy-1+Lin- HSCs. The Examiner has not shown how the cited references teach the genetic modification of these particular HSCs in the presence of the factors and at the concentration ranges recited in the claims." It is noted that these arguments are the same arguments made in the response filed October 12, 2000. The following comments first made in the Office Action mailed 1/4/01 address each of these specific concerns:

In response to these assertions, Examiner cites that following illustrative examples from the cited art that one skilled in the art would have been motivated to specifically use CD34+Thy-1+Lin- HSCs: (a) U.S. Patent 5,750,397 col. 3, para. 3; (b) U.S. Patent 5,744,361 col. 4, lines 4-5; (c) U.S. Patent 5,665,557 col. 3, para. 5 and col. 5, lines 49-61. These references teach that CD34+Thy-1+Lin- are common attributes of HSCs grown in cell culture since these characteristics are used in the isolation process of HSCs from the source tissue. The motivation of one of ordinary skill in the art to grow said cells at specific growth factor concentration ranges recited in the claims is taught by the combination of these and the other prior art references cited. Specifically, the broad claim 18 recites adding an effective amount of a mpl ligand and a flt3 ligand (FL) each at about 0.1 ng/mL to about 500 ng/mL. Claims 23 and 37 recite TPO, FL and IL-6 at about 0.1 ng/mL to about 500 ng/mL. Dependent claims to claim 18 add c-kit from about 5ng/mL to about 200ng/mL, IL3 from about 5ng/mL to about 200ng/mL. Dependent claims to claims 23 add LIF at about 5ng/mL to about 200ng/mL, c-kit from about 5ng/mL to about 200ng/mL, IL3 from about 10ng/mL to about 100ng/mL, and further specify TPO at a concentration of about 5ng/mL to about 200 ng/mL and IL-6 in the range of about 10ng/mL to about 100ng/mL. Dependent claims to claim 37 further specify the following concentrations: TPO, FL and IL-6 all at about 5ng/mL to 200ng/mL; where the concentration of IL3 is about 10ng/mL to about 100ng/mL; where the concentration of c-kit is in the range of 5ng/mL to about 200ng/mL; and where the amounts of TPO and FL and each in the range of about 5ng/mL to about 200ng/mL and IL6 is about 10ng/mL to about 100ng/mL.

As taught in the prior Official Action mailed 4/10/00, pages 3-4, the prior art teaches the use of all of the claimed factors for growth of HSCs. Although no one reference may teach the specific combination of cytokines instantly claimed, the art as a whole clearly teaches that specific composition of HSCs, even selected CD34+Thy-1+Lin- HSCs, vary based on the point at which they were isolated and the growth conditions used (see U.S. Patent 5,665,557 col. 2, para. 5, for instance), which causes differential expression of genes which lead the cells down different paths of growth and thus different outcomes. The use of different cytokine concentration ranges is thus a result of the variance among the isolated cell populations. The story is increasingly complex when one of ordinary skill in the art transforms a population of cells for expressing a transgenic gene so that the cells maintain a certain state of differentiation and gene expression level, or so that the cells will be useful as genetically transformed cells for which the methods of culturing HSCs are generally used for. One of ordinary skill in the art was aware at the time of the instant invention of the motivation to use those cytokines taught in the art on different populations of HSCs in different cytokine concentrations as taught such that the slightly different types of cells were tested with different concentrations of growth factors to optimize the growth (each reference cited teaches unique circumstances to their cell population). The use of ranges of growth factor concentrations of these specific factors was not new either. The specific references cited teach application of each of the claimed factors in comparable ratios absent evidence to the contrary (some of the references teach the Units/mL of the factors, which appear to be in the claimed ranges in view of the open "comprising" language, the "about" language and the "effective amount" language, thus suggesting that since the claim language is open and the references teach effective amounts, the amounts taught in the references read on the instant claims). It was thus argued, that as broadly claimed, the combination of the cited references provides one of ordinary skill in the art with the requisite motivation and expectation of success to make and use the invention as claimed, ie. it was obvious to one of ordinary skill in the art to use the claimed combinations of factors as claimed.

Further, Hanenberg et al. was relied upon to teach the use of fibronectin as a means of optimizing retroviral gene transfer in HSCs and Fletcher et al. was relied upon to teach the use of LIF in the range of 0-1000U/mL to teach that LIF appears to primarily "delay... stem cell commitment to differentiation (p. 844)." These two thus teach optimization of general HSC protocols for the benefits claimed. One of ordinary skill in the art would have had an expectation to see some of the claimed benefits by use of these products in the methods as instantly claimed.

Therefore, it was not by hindsight reconstruction that a rejection was fashioned to read on the instant claimed invention. On the contrary, the cited references broadly teach the use of all the claimed factors for optimized growth of HSCs as cited above and in concentrations which read on the claimed concentrations in view of the open language of the claimed methods. The motivation was taught in the cited references to isolation and grow HSCs in cultures which apply the claimed factors for the functions claimed and having the steps of retrovirally transducing the cells.

As applicant points out, the initial Official Action on the merits mailed 5/12/99 cites the unpredictability in the transgenic stem cell art for expression of transgenes in cultured stem cells. However, the claims at the time of that action broadly claimed any method for promoting the expansion of hematopoietic stem cells in culture and the unpredictability focused on the unpredictability of transforming any hemopoietic cell in the art from any species as broadly claimed. Upon amendment of the claims to specify human cells and a review of the pertinent art, the enablement rejection was withdrawn in view of the instant rejections over the methods of genetically modifying HSCs. As argued above, the art is replete with examples using various cytokine concentrations (which read on the claimed concentrations) such that it would have been obvious at the time the invention was made to practice the invention claimed.